rejection and reconsideration of this application is respectfully requested.

***Rejections under 35 U.S.C. § 102(b)***

Claims 19 and 20 stand rejected under 35 U.S.C. § 102(b) based on the disclosure of Saunders et al. (U.S. Pat. No. 5,066792).

The Examiner stated that no amendment of claim 19 was found in the response filed on January 18, 2000. The Applicants respectfully refer the Examiner to claim 19 on pages 5 and 6 of that response, and specifically to the amendment to step b that appears on page 6, line 5. Amended claim 19 of the present response includes this previously-filed amendment to claim 19 and additional amendments to step b (referring to a "composition consisting essentially of" and a immobilized nucleotide base sequence which forms "directly or indirectly" a stable immobilized hybridization complex, as in claim 6).

An anticipating reference must disclose an invention that does not differ from the claimed invention, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fndn. v. Genetech*, Inc., 927 F.2d 1565, 18 USPQ2d 1001 and 1896 (Fed. Cir. 1991).

The invention of claim 19 includes the steps of (a) providing a biological sample comprising unpurified RNA, (b) mixing the biological sample with a composition consisting essentially of buffer, salt and non-ionic detergent components, where the non-ionic detergent is present in an amount sufficient to release RNA from the biological sample without causing viscosity due to release of chromosomal DNA, and a solid support to which is joined an immobilized oligonucleotide which forms, directly or indirectly, a stable immobilized oligonucleotide:RNA hybridization complex, (c) separating the hybridization complex joined to the solid support from unhybridized sample components, and (d) then washing the hybridization complex with a solution that maintains the hybridization complex.

The Applicants respectfully refer the Examiner to the detailed discussion in the first Amendment, filed January 18, 2000, of the detergent and salt differences between the claimed invention and the method described by Saunders et al. Applicants' claimed method uses a non-ionic detergent that releases RNA from cells without causing viscosity due to release of chromosomal DNA, whereas Sauders et al. disclose (column 5, lines 34-36 and 52-56) use of an ionic (an anionic) detergent in lysis and multiple

centrifugation and resuspension steps to remove DNA. Further, Applicants' claimed invention uses a solution that contains at least about 150 mM of a soluble salt, whereas Sauders et al. disclose (column 5, lines 35-36) using a solution containing 75 mM NaCl and 25 mM $Na_2EDTA$ (i.e., a soluble salt concentration less than the minimum claimed amount). Therefore, the components of the composition used in Applicants' method are not disclosed by Saunders et al.

In addition to these differences, Applicants' method, step b, mixes the biological sample with the buffer, salt and non-ionic detergent components, and with a solid support to which is joined an immobilized oligonucleotide comprising a nucleotide base sequence which forms directly or indirectly a stable immobilized oligonucleotide:RNA hybridization complex. Saunders et al. do not describe such a composition which is mixed with the biological sample. Instead, Saunders et al. disclose merely using a lysis buffer solution that includes an ionic detergent.

In Applicants' claimed method, step c separates the hybridization complex joined to the solid support from unhybridized sample components, and step d washes the hybridization complex joined to the solid support. Saunders et al. do not describe such steps. Instead, Saunders et al. disclose a method that extensively purifies the released RNA and DNA by using multiple extractions with organic chemicals (phenol and chloroform/isoamyl alcohol solutions) followed by ethanol precipitation of the nucleic acid in the aqueous phase (column 5, lines 34-51). Following the purification steps, Saunders et al. further separated RNA from DNA by using multiple resuspension and centrifugation steps (column 5, lines 52-58). Then, Saunders et al. separated the poly(A+)RNA from the purified RNA using multiple oligo(dT) cellulose chromatography separations (column 5, line 59 to column 6, line 17). It is clear from this disclosure that Saunders et al.'s method does not mix the biological sample directly with a composition that includes a solid support having an immobilized oligonucleotide joined thereto to form, directly or indirectly, a stable immobilized oligonucleotide:RNA hybridization complex. Instead, Saunders et al. disclose extensively purifying nucleic acids from a biological sample before chromatography steps are performed. Therefore, Saunders et al. do not disclose all of the steps of Applicants' claimed method.

The Examiner states, on page 2, last sentence of the Office Action, that "any detergent will cause

some viscosity since ... any lysing of a cell will release both types of nucleic acids, DNA and RNA." The Examiner has not provided any support for this statement. To avoid possible "procedural default" and to avoid having this assertion established as "admitted prior art" (*See In re Sun*, 31 U.S.P.Q.2d 1451, 1455 (Fed. Cir. 1993, unpublished)), Applicants request that the Examiner either provide a reference or a declaration under 37 C.F.R. § 1.107(b) in support of this statement. Applicants respectfully disagree with the Examiner's statement because lysis of a *cellular* membrane without substantial lysis of the *nuclear* membrane will cause cell lysis but not release of chromosomal DNA and the resulting viscosity due to release of chromosomal DNA. Applicants respectfully point out that claim 19, step b, specifically refers to "viscosity due to release of chromosomal DNA."

Saunders et al. do not teach every element of the claimed invention and, therefore, cannot anticipate the present invention under 35 U.S.C. §102(b). Applicants respectfully request allowance of amended claim 19 and dependent claim 20.

***Rejections under 35 U.S.C. § 103***

Claims 1-18 have been rejected under 35 U.S.C. §103(a), based on the combined disclosures of Eskola et al. (Clin. Biochem., 1994, 27:373-379), Kacian et al. (US Pat. 5,399,491) and Saunders et al. in view of Rowley et al. (US Pat. 5,487,970), Morris et al. (US Pat. 5,529,925), von Lindern et al. (Molec. Cell. Biol., 1992, 12:3346-3355), Goddard et al. (Science, 29 Nov 1991, pp. 1371-1374), Gruenwald et al. (US Pat. 5,858,682) and Ohki et al. (US Pat. 5,580,727).

In this amendment, claims 1, 6 and 9 have been amended. Claim 6 has been amended in the "contacting" clause consistent with amended claim 19, as discussed above. Claims 1 and 9 have both been amended in step d to clarify that hybridization occurs at "either the first or the second probe binding site" of the second nucleic acid strands.

A *prima facie* case of obviousness requires one to (1) determine the content and scope of the prior art, (2) ascertain the differences between the prior art and the claims at issue and (3) determine the level of ordinary skill in the art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). One of ordinary skill in the art of biotechnology generally has a relatively high level of training. An obviousness determination also

requires consideration of whether the prior art would have suggested to one skilled in the art to make the claimed invention, and would have revealed a reasonable expectation of success in making the claimed invention. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The Examiner is respectfully referred to the discussion of the cited art that appeared in the remarks of the first amendment for details that are not repeated here.

The Examiner has stated it would have been within the ordinary skill of an artisan at the time the invention was made to detect the claimed nucleic acid using one of the probes taught by Eskola et al. Applicants respectfully disagree because the method taught by Eskola et al. *requires* at least two probes for detection: one that binds 5' of and one that binds 3' of a splice junction (Abstract, lines 13-16; page 374, col. 1, lines 14-16 and p. 375, col. 2, lines 26-31). The method taught by Eskola et al. requires one probe to bind the detected sequence to a solid surface, and one detectable labeled probe that binds to the bound complex (page 375, col. 2, lines 23-48). If only one of the probes taught by Eskola et al. is bound to the sequence to be detected, the sequence cannot be detected because it will either be unlabeled (i.e., if only the probe that binds the sequence to the solid surface is bound) or it will appear indistinguishable from a mixture that includes unbound labeled probe and the spliced sequence to be detected or an unspliced related sequence (i.e., if only the labeled probe is bound). Thus, the method taught by Eskola et al. requires that both probes be bound and cannot suggest Applicants' methods in which a probe binds to *either* the first or the second probe binding site, as in claim 1, step d, and claim 9, step d. Eskola et al., in fact, teach away from hybridizing to only one probe binding site because the method of Eskola et al. would be inoperative if only one site was hybridized to a probe.

The Examiner stated on page 3, last sentence of the Office Action that "the two probes taught by Escola et al. for amplification of the nucleic acid target read on the limitations of the [present] claims for 'a first probe binding site ... and a second probe binding site' and therefor read on the claims as written." The Applicants assume that the Examiner is referring to the language that appears in claim 1, step c and claim 9, step c. Applicants respectfully point out that the "first probe binding site" and the "second probe binding site" defined in claims 1 and 9, step c, define the positions of these sites relative to each other and other

elements of the second nucleic acid strand. Step d of both claims 1 and 9 make clear that the hybridizing step uses only one of these sites, i.e., either the first or the second probe binding site. Therefore, Applicants respectfully submit that Eskola et al. do not suggest to one skilled in the art to make the present invention. Moreover, using the teachings of Eskola et al., one skilled in the art, at the time the invention was made, would not have predicted success for Applicants' claimed invention because success, based on the teachings of Eskola et al., would only result if *both* probe binding sites were simultaneously used in the hybridization and detection steps.

Therefore, Applicants respectfully submit that the present invention is not made obvious by the teachings of Eskola et al. in combination with any of the other cited art.

The Examiner stated that the initial statement in the Background section of Kacian et al. (column 1, lines 33-40) provides motivation that suggests detection of chromosomal abnormalities in a sample as presently claimed. The statement from Kacian et al. indicates that detection and quantitation of nucleic acid sequences is an increasingly important technique with a number of applications, including detecting genetic abnormalities. Applicants, however, submit that this general statement on the importance of such techniques would not motivate one skilled in the art to make the particular combination of steps claimed in Applicants' invention. Nor would it, even if combined with other parts of the Kacian et al. disclosure and the other cited art, have revealed a reasonable expectation of success in making the claimed invention to one skilled in the art at the time Applicants' invention was made.

Applicants respectfully refer the examiner to the detailed discussion of Rowley et al., Morris et al., Gruenwald et al., von Lindern et al., Ohki et al. and Goddard et al. that appeared in the first Amendment. These references disclose methods of detecting genetic rearrangements, specific fusion or chimeric sequences, and detection of a chimeric protein, and have been cited as teaching motivation in the art to detect specific genetic translocations claimed in dependent claims. Applicants, however, contend that a prima facie case of obviousness has not been established with regard to the inventions defined by independent claims 1 and 9. Thus, any motivation provided by the Rowley et al., Morris et al., Gruenwald et al., von Lindern et al., Ohki et al. and Goddard et al. references to detect specific translocations cannot

render the dependent claims obvious. Similarly, the Examiner is respectfully referred to the detailed discussion of the Saunders et al. reference discussed in the remarks related to the §102(b) rejections above, which for the reasons discussed above also does not suggest the methods of dependent claims 6-8. Therefore, Applicants respectfully request allowance of dependent claims 2-8 and 10-18.

For the foregoing reasons, Applicants respectfully request withdrawal of the rejections based on 35 U.S.C. § 103 and request that claims 1-18 be allowed.

## CONCLUSION

In view of the foregoing amendments and remarks, the Applicants respectfully submit that the claims, as amended, are patentable and in condition for allowance. Accordingly, withdrawal of the rejections and allowance of the application is earnestly solicited. The undersigned has made a good-faith effort to address all the points raised in this Office Action and to place the claims in condition for allowance. If minor matters remain that could be resolved by telephone interview, the Examiner is invited to contact the undersigned at the number below.

Applicants believes there is no fee due in connection with the filing of this Amendment. However, if Applicants are in error and a fee is required, please debit Deposit Account No. 07-0835 the appropriate amount.

Respectfully submitted,

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